REMARKS

Support for the amendment to define the compounds more precisely in claims 1 and 21 is found at pages 2 - 5 of the specification and original claim 20. Support for the time of administration of the compounds in claim 21 and for new claim 41 is found at the top of page 2 of the specification.

The Examiner has rejected claims 1, 3-5, 21, 22, 24-26, 39 and 40 under 35 USC 112, first paragraph, as failing to comply with the written description and enablement requirements. Claims 1 and 21 have been amended to specify that the compounds used are those which are effective in the treatment of Alzheimer's disease, namely galanthamine, lycoramine, analogs of these two compounds and rivastigmine. The examiner discusses the Wands factors. However, it is submitted that with this limitation, the applicant clearly had possession of the claimed invention at the time of filing the application and one skilled in the art will have no difficulty in carrying out the invention throughout its claimed scope.

Therefore, it is respectfully requested that the 35 USC 112 rejections should be withdrawn.

The Examiner has rejected claims 1, 3-5, 7-21, 22, 24-26, and 28-38 under 35 USC 103(a).

The essence of the present invention lies in the provision of a composition and method that will enable one suffering from Alzheimer's disease to be able to take acetyl cholinesterase inhibitors, compounds known to be useful in the treatment of the disease while avoiding the adverse effects that these drugs have on sleepand circadian rhythms. This is accomplished by selection of those drugs that have a half-life of such duration that the most of it can be metabolized into a product that does not hinder sleep prior to the patient's next anticipated sleep period, by formulating the drug in such a way that it can be administered prior to sleep but

only start to be released at the time when the patient starts to awake and by administering the drug at a time that takes advantage of these two factors. Nothing in the prior art taken either singly or in combination points to the possibility of overcoming the sleep problems of those being treated with acetyl cholinesterase inhibitors in this way. The problem solved by the present invention is one that has been known for many years. The effects of acetyl cholinesterase activity have been known since 1974 as is shown by

Acetylcholinesterase activity, which keeps synaptic acetylcholine concentrations low, peaks during the subjective night, and is lowest during activity periods. (Schiebeler, 1974, referred to in the present application on page 5 three lines from the bottom of the page); and

Cholinesterase inhibitors administered during sleep produce awakenings. (Sitaram, 1979, referred to in the present application at page 6 five lines from top

Copies of these articles are attached.

However despite this knowledge, prior to the present invention, no one had taught to formulate or administer acetyl cholinesterase inhibitors so as to ensure that they were not active during sleep.

Turning now to the prior art cited by the examiner:

Shapiro is but one representative of body of prior art that teaches the use of certain acetyl cholinesterase inhibitors for the treatment of Alzheimer's disease.

Conte states that "there is an increasing awareness that the drug must be administered not only in the right amount at a proper rate but also at the right time." Conte then refers to drugs such as antiasthmatic, anti-histaminic, psychotropic, anaesthetic, cardiovascular active drugs, NSAIDs, etc. that have significant daily variations in pharmacokinetics and/or drug effects have been demonstrated in man, depending on physiological and/or physiopathological changes of circadian rhythmicity. Conte then gives the example of asthma and hypertension and states that an asthmatic attack generally happens in the early morning and that in hypertension diseases the pressure value is higher during the daytime. The teaching of Conte is directed to drugs that should be administered at a specific time of day in order to have the most beneficial effect "to fulfil the specific

therapeutic needs of such diseases, which depend on circadian rhythmicity, new drug-delivery devices are required..."

This differs from the invention claimed in this application wherein the time of delivery of a formulation of acetyl cholinesterase inhibitors is not of any particular significance. As stated as an example in the previous response, Alzheimer's does not have diurnal variation and treatment is not controlled by circadian rhythm. What the present invention does is to take steps to prevent certain effects taking place at a time when they are undesired rather than formulating a product to have positive effects at a desired time. Nothing in the prior art points to such a possibility.

Nothing in Brossi overcomes this basic defect in the prior art. Brossi discusses the use of physostigmine, an acetyl cholinesterase inhibitor, in treatment of Alzheimer's disease and describes formulations containing physostigmine. However, there is nothing in this disclosure to point to selection of a drug with a particular half life (physostigmine's is 25 to 30 minutes see Whelpton et al J. Chromatography 341 (1985) 361 – 371 page 370 paragraph 3 – copy enclosed) and so falls outside the definition in the present claims) or to utilize a formulation of the drug where the delay in release is chosen to correlate with circadian rhythms so as to avoid certain effects at certain times. In particular there is no teaching of avoidance of activity during sleeping, nor of the importance of selecting a compound having an appropriate half-life.

There is no motivation to combine Conte with either Brossi or Shapiro and any attempt to do so is based on hindsight. Furthermore, as stated above there is no disclosure or suggestion in the combination of these references of a dosage form wherein the acetylcholinesterase has a half life of from one to eleven hours and is formulated so as to delay its activity for a predetermined period of from four to twelve hours.

Rhythms and Drug Delivery (Journal of Controlled Release, 16:63-74, 1991)

tabulates "Drugs for which daily variations in their effects were reported in clinical studies" (Table 2, page 69). This list covers cardiovascular active drugs, anticancer drugs, miscellaneous, antiasthmatic drugs, psychotropic drugs, H1 antihistamines, NSAIDS, general and local anesthetics and opioids and endocrinology/gastroenterology drugs, while specifically naming 82 compounds. Metacholine is listed under "antiasthmatics" and this presumably refers to a diurnal variation in the bronchial response to inhaled methacholine. No cholinesterase inhibitor or Alzheimer treatment is listed.

A copy of the article is enclosed.

Neurology carried an article in 2001 (Doody et al Practice parameter: Management of dementia (an evidence-based review, Neurology 2001; 56; 1154-1166 – copy enclosed)) which reviews the state of the art in treatment of dementias such as Alzheimer's disease. This article noted (page 1157) that there were different side effects with the different acetyl cholinesterase inhibitors that were effective. However, it did not indicate what they were or that any steps could be taken to address such side effects. This article which is a good representation of the state of the art at the time of filing the application therefore shows that the art had not appreciated the possibility of solving the problem solved by the present invention, let alone what that solution might be.

Therefore, it is respectfully requested that the rejections under 35 USC 103 be withdrawn.

Applicant has become aware of European Patent 1140105 having a later priority date than the present application. This is enclosed to ensure compliance with applicant's duty of disclosure although it has a later priority than the present application. The prior art considered it its prosecution is listed on the front page and is also enclosed herewith.

Applicant submits that the present application is in condition for allowance

and favorable consideration is respectfully requested.

Respectfully submitted,

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